# Predicting a complicated course of *Clostridium difficile* infection at the bedside

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## Abstract

*Clostridium difficile* infections (CDIs) are a common cause of antibiotic-associated diarrhoea and associated with CDI-related mortality in *c.* 10%. To date, there is no prediction model in use that guides clinicians to identify patients at high risk for complicated CDI. From 2006 to 2009, nine Dutch hospitals included hospitalized CDI patients in a prospective cohort. Potential predictors of a complicated course (ICU admission, colectomy or death due to CDI) were evaluated in uni- and multivariate logistic regression. A score was constructed that was internally validated by bootstrapping. Furthermore, a pilot external validation was performed. Twelve per cent of 395 CDI patients had a complicated course within 30 days after diagnosis. Age (≥85 years, OR 4.96; 50–84 years, 1.83), admission due to diarrhoea (OR 3.27), diagnosis at the ICU department (OR 7.03), recent abdominal surgery (OR 0.23) and hypotension (OR 3.25) were independent predictors of a complicated course. These variables were used to construct a prediction model. A score subsequently classified patients into high risk (39% with a complicated course), intermediate (16%), low (5%) or virtually no risk of experiencing a complicated course. The score performed well after internal validation (AUC 0.78) and a pilot external validation among 139 patients showed similar good performance (AUC 0.73). We present an easy-to-use, clinically useful risk score that is capable of categorizing CDI patients according to their outcome. Because classification is available at diagnosis, it could have major implications for treatment choice.

**Keywords:** CDI, *Clostridium difficile* infection, complicated course, mortality, prediction rule
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## Introduction

*Clostridium difficile* infection (CDI) commonly presents as a colitis, which occurs when toxin is produced by the bacterium. Symptoms may include cramps, fever, abdominal pain or signs of an ileus or peritonitis; diarrhoea is almost always present. Inflammation of the gut may be so severe that hypotension, perforation or a toxic megacolon occurs [1,2]. The number of patients that die as a consequence of CDI increased when a virulent *C. difficile* strain, PCR ribotype 027, emerged in 2002. CDI is now found to increase the absolute risk of death within 30 days by *c.* 10% [3,4].

Vancomycin and metronidazole are currently the most frequently used drugs to treat CDI, but newer treatment options, such as the recently licensed drug fidaxomicin, are now available [5]. This drug has been shown to be as effective as vancomycin in the treatment of CDI, but the population that benefits most from this new but costly treatment remains to be determined. In patients with severe CDI, vancomycin treatment is superior to metronidazole [6,7]. Because severe symptoms are associated with a complicated course (e.g. death), it is important to identify patients at risk of a complicated course and use this as a guide towards treatment [2,8]. In an attempt to

characterize patients who die due to CDI, several risk factors have been described, including advanced age, concomitant use of antibiotics, fever, admission to the intensive care unit and presence of leucocytosis, elevated creatinine or low serum albumin [6,9–14]. Furthermore, *C. difficile*-specific factors such as PCR ribotype have been associated with mortality due to CDI [10]. In spite of the detection of useful predictors of a complicated course, no clinically useful prediction model has been constructed to date [15].

In this study, we aim to define prognostic markers for a complicated course of CDI, using variables that are available at a patient's bedside at time of diagnosis. Next, we aimed to develop an easy-to-use prediction rule that could help physicians to identify patients at risk of a complicated course of CDI.

## Patients and Methods

### Patient selection

From March 2006 to May 2009, nine Dutch hospitals (five academic and four community) prospectively included hospitalized patients with CDI in a cohort study. Hospitals participated for a minimum of six consecutive months in the 3-year study period. Patients from all departments and co-morbidities were considered eligible. CDI was defined as the presence of diarrhoea (≥3 unformed stools per 24-h period) and a positive *C. difficile* toxin test. In addition to testing because the treating physician suspected CDI, all patients with diarrhoea who were hospitalized for 2 or more days were routinely tested for *C. difficile*. The toxin test that was used differed per hospital according to the local standard. Four hospitals used the ImmunoCard Toxins A&B (Meridian Bioscience, Cincinnati, OH, USA), three used a cytotoxicity assay, one used the Premier Toxins A&B (Meridian) and another hospital used the VIDAS *C. difficile* A&B test (bio-Merieux, Marcy-l'Etoile, France). For every patient, only a single inclusion in the study was possible. The study was approved by the Institutional Review Ethics Boards.

### Data collection

Patient information was collected by a study physician (AG) and registered on a standardized questionnaire, using patient records, the electronic medical information system and by consulting the physician in charge. Demographic characteristics such as age, sex, hospital and department of diagnosis were collected. Information on risk factors for CDI present in the 3 months prior to the onset of diarrhoea was collected and included previous medication (antibiotics, immunosuppressive agents, chemotherapeutic agents, antacids and proton-pump inhibitors) and hospital admissions. Data concerning underlying medical conditions were classified using the 10th edition of the International Classification of Diseases and the Charlson's Co-morbidity Index [16]. At the day of diagnosis (plus or minus 1 day), signs and symptoms during physical examination were recorded: fever (temperature >38.5°C), macroscopic blood in the stool, hypotension (systolic blood pressure below 100 mmHg and/or diastolic blood pressure below 60 mmHg) and abdominal pain. Serum creatinine was recorded before the onset of diarrhoea.

Variables had missing data in <3% of patients, except for fever, hypotension and bloody diarrhoea, which were incomplete in 10–13%. Creatinine values were not registered in one hospital (13%). To account for missing data in multivariable analysis, values were imputed using multiple imputation. This method is appropriate when values are missing at random (MAR) [17], which seemed reasonable to assume in our study because variables that were predictive of the missing data were determined. All potential predictors, the outcome variable and nine additional variables were included in the imputation procedure.

Submission of *C. difficile* isolates to the LUMC was requested from all participants; however, one hospital submitted no samples and two others submitted only a few (<1/3). Submitted isolates were cultured on selective plates for *C. difficile* after an alcohol shock and identified as *C. difficile* by the detection of the *glu*D gene by PCR. All positive isolates were PCR-ribotyped as previously described [18,19].

### Outcome measurement

Thirty days after diagnosis the course of CDI was considered by consensus of the treating physician and a study physician (MH or AG). A complicated course was defined according to international recommendations [20,21]: (i) death as a direct or indirect consequence of CDI, (ii) (prolonged) admission to the intensive care unit due to CDI, (iii) colectomy due to CDI. Survival status of all patients was checked using the Dutch Civil Registration System in which all Dutch inhabitants are registered.

### Predictors of a complicated course of CDI

Based on previous research we selected potential predictors of a complicated course of CDI that could be obtained at time of diagnosis, including age, department of diagnosis, use of antibiotic agents, Charlson's Co-morbidity Index and creatinine count [3,10–12,22,23]. Additionally, we selected sex, hospital of diagnosis (academic or community), location of onset of diarrhoea (healthcare or community), reason for admission (diarrhoea or other), some well-known risk factors for acquiring CDI (medication and interventions) and signs and symptoms that were recorded during physical examination as

potential predictors, with the exception of abdominal pain, which was deemed too subjective. Potential predictors were analysed using univariate logistic regression analysis. Multivariable logistic regression was performed for all potential predictors with a p-value <0.50 in univariate analysis. Subsequently, the model was reduced by stepwise excluding variables with a p-value of >0.10 based on the log likelihood ratio test (backward selection). Therefore, the strongest predictors remained in the final model. Results were displayed as odds ratios (ORs).

#### Prediction rule development, performance and internal validation

Any prognostic model shows a too optimistic performance in the dataset from which it is developed (over-fitting) [24]. To adjust for this optimism and to validate the model, we used bootstrapping techniques. During this process, the model is constructed numerous times ($n$ = 200) using a subset of the dataset to predict the outcome of the other part of the dataset. This way, the optimism can be quantified with a number (shrinkage factor). The regression coefficients of the final model were multiplied with the shrinkage factor and subsequently rounded to integers to construct a simple prediction rule. For each patient we calculated a summed score. The discriminative ability of our model was expressed by calculation of the area under the receiver operating characteristic curve (ROC area), which ranges from no discrimination (0.5) to perfect discrimination (1.0). Calibration of the original model was evaluated by using the Hosmer and Lemeshow test. A simplified version of the prognostic rule was constructed to divide patients into low, medium and high-risk categories. Similarly, this simplified rule was tested for its discriminative ability, sensitivity and specificity. Furthermore, performance was assessed by calculating the positive and negative predictive values and diagnostic accuracy.

#### Sensitivity analyses and pilot external validation

Several sensitivity analyses were performed, including (i) restriction to patients aged ≥15 years, (ii) restriction to patients who were treated for CDI with metronidazole and (iii) a complete case analysis. A small cohort ($n$ = 139) was used as a pilot of external validation. This cohort consisted of all CDI patients diagnosed between May 2009 and May 2011 in a single hospital (Radboud University Medical Center, Nijmegen, the Netherlands). This hospital also participated in the derivation study between 2006 and 2009; definitions of CDI and outcome were equal to those used to construct the prediction rule.

Analyses were carried out using PASW Statistics version 17.0 (SPSS Inc., Chicago, Illinois, USA) and R version 2.12.2, package Design and pROC (The R Foundation for Statistical Computing, Vienna, Austria).

## Results

In total, 395 patients with CDI were included. Their median age was 65 years (IQR 52–77); 55.7% of the population was male. Three months prior to the onset of diarrhoea, 85.0% had used antibiotic therapy and 54.7% had been admitted to a healthcare facility. Abdominal pain (54%), fever (60%) and hypotension (30%) were frequently present at the time of diagnosis, whereas bloody diarrhoea (15%) was present in a minority of the patients. Patient characteristics are displayed in Table 1.

Within the first 30 days after diagnosis, 88.2% of the patients received antibiotic treatment for CDI. Most frequently, metronidazole was used (74.3%). A combination of metronidazole and vancomycin was used in 11.3% and vancomycin monotherapy in 2.6%. Sixty-five patients (16.5%) died within 30 days after the diagnosis; 38 (9.9%) of these deaths were related to CDI. Five patients had a colectomy and three were admitted to the intensive care unit due to CDI; therefore, a complicated course due to CDI was observed in 46 patients (11.9%).

The PCR ribotype causing CDI was known for 207 of the 225 samples (92.0%) that were submitted for typing (52.4% of all patients); the most frequently found types were 014 (16.9%), 078 (12.1%), 001 (8.7%) and 027 (8.2%). As described in detail elsewhere [25], type 027 was associated with the highest 30-day mortality risk (29%).

#### Prediction rule

Seventeen variables were selected as potential predictors and included in univariate analysis (Table 1). Age, department of diagnosis, admission to an academic hospital, recent abdominal surgery, the prior use of antibiotic agents, diarrhoea as a reason for admission and hypotension were significantly associated with a complicated course of CDI after 30 days in this analysis. Sex, prior use of cytostatic or immunosuppressive agents, bloody diarrhoea and Charlson's Co-morbidity index, were discarded after univariate analysis due to a p-value of >0.50. The remaining 12 variables were included in multivariable logistic regression. After reduction of the model by backward selection, five variables remained strongly associated with a complicated course of CDI: age (OR 4.96 for age ≥85 years; OR 1.83 for age 50–84 years), department of diagnosis (OR 0.98 for surgery; OR 7.03 for the ICU department), recent abdominal surgery (OR 0.23), hypotension (OR 3.25) and admission because of diarrhoea (OR 3.27; Table 2). Calibration of this model was good (Hosmer Lemeshow test p = 0.36 in the original dataset). The

**TABLE 1. Univariate analysis of potential predictors for the development of a complicated course due to CDI**

| | CDI patients ($n$ = 395) | | Severe course due to CDI[a] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Yes | | No | | | |
| | $n$ | % | $n$ | % | $n$ | % | Odds ratio (95% CI) | p-value |
| Demographic characteristics | | | | | | | | |
| Age | | | | | | | | |
| <49 years | 85 | 22 | 6 | 13 | 79 | 23 | 1 (reference) | 0.01 |
| 50–84 years | 275 | 70 | 31 | 67 | 237 | 70 | 1.72 (0.69–4.28) | |
| >85 years | 35 | 9 | 9 | 20 | 23 | 7 | 5.15 (1.66–16.0) | |
| Male sex | 220 | 56 | 24 | 52 | 191 | 56 | 0.85 (0.46–1.57) | 0.59 |
| Academic hospital | 266 | 67 | 23 | 50 | 239 | 71 | 0.42 (0.22–0.78) | 0.01 |
| Department of diagnosis | | | | | | | | |
| Other departments | 293 | 74 | 35 | 76 | 251 | 74 | 1 (reference) | <0.01 |
| Surgery | 83 | 21 | 4 | 9 | 78 | 23 | 0.37 (0.13–1.07) | |
| Intensive Care Unit | 19 | 5 | 7 | 15 | 10 | 3 | 5.02 (1.80–14.0) | |
| Medication and intervention history[b] | | | | | | | | |
| Cytostatic agents | 64 | 16 | 7 | 15 | 55 | 16 | 0.91 (0.39–2.15) | 0.84 |
| Immunosuppressive agents | 172 | 44 | 21 | 47 | 146 | 44 | 1.13 (0.60–2.10) | 0.71 |
| Proton pump inhibitors | 251 | 64 | 34 | 76 | 211 | 63 | 1.82 (0.89–3.71) | 0.10 |
| Recent abdominal surgery | 110 | 28 | 4 | 9 | 105 | 31 | 0.21 (0.07–0.59) | <0.01 |
| Recent admission | 210 | 55 | 28 | 61 | 177 | 54 | 1.37 (0.71–2.49) | 0.38 |
| Antibiotic agents | 335 | 85 | 34 | 74 | 293 | 87 | 0.44 (0.21–0.90) | 0.03 |
| Clinical characteristics | | | | | | | | |
| Charlson Index | | | | | | | | |
| 0 | 59 | 15 | 7 | 15 | 52 | 15 | 1 (reference) | 0.53 |
| 1–2 | 150 | 38 | 14 | 30 | 134 | 40 | 0.78 (0.30–2.03) | |
| 3–4 | 120 | 31 | 15 | 33 | 101 | 30 | 1.10 (0.42–2.87) | |
| >5 | 64 | 16 | 10 | 22 | 50 | 15 | 1.49 (0.53–4.21) | |
| Diarrhoea as reason for admission | 104 | 27 | 23 | 50 | 78 | 23 | 3.31 (1.76–6.22) | <0.01 |
| Healthcare onset diarrhoea | 283 | 72 | 28 | 61 | 248 | 74 | 0.55 (0.29–1.04) | 0.06 |
| Fever | 208 | 60 | 25 | 66 | 174 | 59 | 1.36 (0.67–2.76) | 0.40 |
| Hypotension | 117 | 30 | 25 | 63 | 88 | 30 | 3.86 (1.94–7.68) | <0.01 |
| Bloody diarrhoea (macroscopic) | 52 | 15 | 7 | 16 | 44 | 15 | 1.14 (0.48–2.71) | 0.77 |
| Laboratory parameter | | | | | | | | |
| Creatinine count prior to start of diarrhoea | | | | | | | | |
| <90 | 199 | 58 | 17 | 43 | 178 | 61 | 1 (reference) | 0.05 |
| >90 | 109 | 32 | 16 | 40 | 89 | 30 | 1.88 (0.91–3.90) | |
| Dialysis | 33 | 10 | 7 | 18 | 25 | 9 | 2.93 (1.11–7.77) | |

[a]Outcome is missing for 10 patients (2.5%), therefore the maximum number of patients is 46 with a severe course and 339 without a severe course.
[b]Medication and intervention history was gathered from the 3 months prior to the start of diarrhoea.

**TABLE 2. Strongest independent predictors of a complicated course of CDI in multivariable analyses**

| | Odds ratio (95% CI) | p-value | Regression coefficient before shrinkage | Regression coefficient after shrinkage | Score |
|---|---|---|---|---|---|
| Age | | | | | |
| ≤49 years | 1 (reference) | Reference | 0.00 | 0.00 | 0 |
| 50–84 years | 1.83 (0.68–4.97) | 0.24 | 0.61 | 0.52 | 1 |
| ≥85 years | 4.96 (1.40–17.6) | 0.01 | 1.60 | 1.38 | 3 |
| Department of diagnosis | | | | | |
| Other departments | 1 (reference) | Reference | 0.00 | 0.00 | 0 |
| Surgery | 0.98 (0.30–3.17) | 0.97 | −0.02 | −0.02 | 0 |
| Intensive Care Unit | 7.03 (2.02–24.4) | <0.01 | 1.95 | 1.68 | 3 |
| Recent abdominal surgery | 0.23 (0.07–0.73) | 0.01 | −1.47 | −1.26 | −3 |
| Hypotension | 3.25 (1.53–6.91) | <0.01 | 1.18 | 1.01 | 2 |
| Diarrhoea as reason for admission | 3.27 (1.57–6.80) | <0.01 | 1.18 | 1.01 | 2 |

These predictors, selected in multivariable analyses, were included in the final model. Their regression coefficients were shrunk in order to correct for optimism and subsequently a score was developed. The chance that an individual patient develops a complicated course due to CDI can be predicted by the following formula: $p = 1/(1 + \exp(-3.15 + 0.52 \times \text{age } 50\text{–}84 + 1.38 \times \text{age } \geq 85 + 0.02 \times \text{department of surgery} + 1.68 \times \text{department of ICU} + 1.26 \times \text{recent abdominal surgery} + 1.01 \times \text{hypotension} + 1.01 \times \text{diarrhoea as a reason for admission}))$.

regression coefficients of these variables were multiplied by 0.86 (shrinkage factor), after which they were converted into a score. For each patient the total score was calculated, ranging between −3 and 10. All 395 patients were stratified according to their summed score in Table 3. No patients had a summed score of >8. The observed probability of developing a complicated course due to CDI was calculated for each stratum, which showed that a high score correlated with a high risk of development of a complicated course of CDI and vise versa (Table 3).

Based on these results, four risk categories were defined: no risk (<0 points), low risk (0–1 points), medium risk (2–3 points) and a high risk (≥4 points) of developing a complicated course of CDI. A patient that is categorized in the highest group has *c.* 40% chance of developing a complicated course, whereas a patient categorized in the lowest group has virtually no chance of developing a complicated course due to CDI. After internal validation of the model, the ROC area was 0.80 (0.73–0.86) for the complete and 0.78 (0.71–0.85) for the simplified risk score.

**TABLE 3. Derivation of the risk score: predicting a complicated course of CDI**

| Completescore | Patients (*n*) | Observed complicated course (%) | Simplified score | Patients (*n*) | Observed complicated course (CI 95%) | |
|---|---|---|---|---|---|---|
| −3 | 15 | 0 | | | | |
| −2 | 40 | 0 | <0 | 63 | 0% | – |
| −1 | 7 | 0 | | | | |
| 0 | 65 | 3 | 0–1 | 156 | 5% | (2–9%) |
| 1 | 92 | 7 | | | | |
| 2 | 26 | 11 | 2–3 | 121 | 17% | (10–23%) |
| 3 | 95 | 18 | | | | |
| 4 | 7 | 34 | | | | |
| 5 | 35 | 32 | | | | |
| 6 | 3 | 31 | ≥4 | 55 | 39% | (26–52%) |
| 7 | 6 | 63 | | | | |
| 8 | 3 | 100 | | | | |

**TABLE 4. Performance of the simplified risk score, using three different cut-off points to define a complicated course**

| | Cut-off point for a complicated course | | |
|---|---|---|---|
| | ≥0 | ≥2 | ≥4 |
| NPV | 1 | 0.96 | 0.92 |
| PPV | 0.15 | 0.24 | 0.39 |
| Sensitivity | 1 | 0.84 | 0.43 |
| Specificity | 0.18 | 0.61 | 0.90 |
| Accuracy | 0.28 | 0.64 | 0.84 |

NPV, negative predictive value; PPV, positive predictive value.

Using our prediction rule, several cut-off points can be used to define patients as 'at risk of a complicated course'. Sensitivity and specificity were 84% and 61%, respectively, for a cut-off point of ≥2, which changed to 43% and 90% for a cut-off point of ≥4. Performance of the prediction rule using different cut-off points is displayed in Table 4.

#### Sensitivity analyses and pilot external validation

We performed sensitivity analyses on two different patient selections: patients treated with metronidazole only and patients aged ≥15 years old (95% of the original cohort). Furthermore, we performed a complete case analysis in which 260 patients (66%) were eligible for multivariable analysis and 326 patients (83%) had complete data for the final prediction rule. All analyses yielded the same strongest five predictors of a complicated course due to CDI: diarrhoea as a reason for admission, department of diagnosis, age, recent abdominal surgery and hypotension; identical to the predictors selected in the original analysis. Furthermore, similar ROC areas were found (≥0.77 in both selected patient groups and the complete case analysis).

A pilot for external validation was performed in a cohort of 139 patients. Seven of these patients (5.0%) developed a complicated course of CDI within 30 days after diagnosis. Although numbers were limited, a higher score corresponded with a higher chance of a complicated course: patients with score <0 ($n$ = 18) had a 0% chance of experiencing a complicated course, score 0–1 ($n$ = 55) had a 4% chance, score 2–3 ($n$ = 52) had a 4% chance, and score ≥4 had a 21% chance ($n$ = 14). The risk score also performed relatively well, with an AUC of 0.73 and a sensitivity and specificity of 43% and 92%, respectively, at a cut-off point of ≥4.

## Discussion

In the literature, *C. difficile* infections are associated with high mortality risks of around 10% in the first 30 days [3,4]. In our study, the CDI-related mortality was also 10%, and 12% of the CDI patients experienced a complicated course within 30 days after diagnosis. A complicated course was associated with advanced age, admission because of diarrhoea and diagnosis in the ICU department. Furthermore, recent abdominal surgery (negative predictor) and hypotension were independent predictors of a complicated course. Here, we present a multivariable risk score for a complicated course of CDI, composed of these factors, which are easily accessible at diagnosis. The score can distinguish patients with a high risk (39%) of developing a complicated course from those who have an intermediate risk (16%), low risk (5%) or virtually no risk of developing a complicated course.

Several studies previously attempted to construct prediction rules and classify patients according to their outcome. However, none of these rules reached clinical practice due to small sample sizes and the lack of internal or external validation [15]. Two of 13 published prediction rules on the outcome of CDI were validated, however, the inclusion of subjective parameters (altered mental status) and parameters that are not available at diagnosis (radiologic findings) limited their use [26–29]. A validated risk score using recurrences as an outcome does exist [30], though its value is questioned because it was constructed with <50 patients in the derivation and validation cohorts. Our prediction rule is internally

validated and based on simple, clinical parameters that are available after completion of history and physical examination. This enables the physician to use it at a patient's bedside and on time for treatment guidance.

The prediction rule we present here is capable of defining a high-risk population: the positive predictive value rises from 12% (prevalence of a complicated course in the CDI population) to 39% when a cut-off of ≥4 is used. This high-risk population is in strong need of treatment options other than metronidazole and might benefit most from novel but expensive treatments. Current evidence favours vancomycin above metronidazole in patients with severe symptoms of CDI [6]; therefore, it is likely that the high-risk group benefits from vancomycin. Overall, our prediction rule could guide more diverse treatment modalities; however, the exact threshold (e.g. cut-off of ≥4 or ≥2) for a treatment other than metronidazole should be determined based on careful consideration regarding the harms vs. the benefits of the treatment. It should be emphasized that the majority of our patients were treated, including those with approximately no chance of developing a complicated course. This prediction rule therefore does not recommend watchful waiting in patients with a low risk of experiencing a complicated course.

Advanced age has frequently been associated with mortality and a complicated course of CDI [11,31–35]. Diagnosis in the ICU department [36] and hypotension [33,36–38] have also been associated with a complicated course in previous research. A quarter of the patients in our study were admitted because of diarrhoea, which was associated with a complicated course after 30 days. Morrison *et al.* [35] found a similar percentage and association in their large cohort of 485 patients and hypothesized that this could be due to a more complicated course of community-acquired infections. In our population, however, 63% of the patients who were admitted because of diarrhoea had been admitted to a healthcare facility in the preceding 3 months and therefore did not have community-acquired infection. We hypothesize that admission due to diarrhoea is a proxy for patients with severe symptoms and consequently at risk of a complicated course. Patients with recent abdominal surgery less frequently experienced a complicated course in our study. Several studies report this [11,32,39] and the explanation of Bhangu *et al.* [32] is that these patients are probably often younger and fitter compared with patients without recent surgery. This explanation seems reasonable; however, in our study the mean age (59.5 vs. 61.9 years) and Charlson's Co-morbidity Index (category of ≥5, 14.5% vs. 17.3%) only slightly differ between patients with vs. without previous surgery. Therefore, other yet unknown factors probably contribute to the difference between patients with and without recent abdominal surgery.

Serum creatinine was related to a complicated course in univariate analysis; however, it was discarded after multivariable analysis. Other laboratory parameters, such as a hypoalbuminaemia and leucocytosis, were in our study not measured at diagnosis but during the course of the disease. We recently concluded that timing of these measurement highly influences the usefulness of these laboratory predictors [40]. For this reason, these potential predictors were not included in our analysis. Rapid subtyping of *C. difficile* is unavailable in most laboratories and typing data are not available at diagnosis. The presence of a hypervirulent strain such as PCR ribotype 027 was therefore not evaluated as a potential predictor in our analysis.

Although our prediction rule is constructed using strong methodology and is based on a clinically relevant outcome, our study has several limitations. First of all, the measurement of outcome is based on clinical judgement, which can be subjective. To minimize ascertainment bias, outcome was based on the consensus of two physicians and death within 30 days was verified by using the highly reliable Dutch National Registration System. Additionally, we used tests with different sensitivities and specificities to construct our cohort, which could have influenced our study population, and therefore the mortality risk (more sensitive tests were associated with a higher mortality risk in our study; data not shown). However, as many hospitals still use 'insensitive' enzyme immunoassays in the Netherlands, our study is likely to represent the mortality among CDI patients in Dutch hospitals [CID]. Although our model performed well after internal validation (AUC 0.78) and a small external validation, its generalizability should be tested again in a setting with different researchers, locations and time. Interestingly, in our derivation and pilot-validation cohorts, the frequency of a complicated course differed (12% and 5%, respectively). Pilot-validation was carried out in a single centre that also had a better survival during the derivation period (when 8% of the patients had a complicated course), which explains the difference.

In summary, we present a multivariable risk score that is designed to identify patients who are at risk of a complicated course of CDI. Because these patients might benefit from a different treatment, classification of patients according to their outcome could have major implications. Guidance of treatment decisions and selection of high-risk patients as a target population for new, but expensive, treatments may be one of the future applications [5]. Additionally, the populations of different trials can now be compared and our score enables surveillances to more objectively classify patients at risk of a complicated course of CDI. External validation and determination of the clinical threshold for initiating the complicated course treatment are aims for further research.

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## Reporting

This study was reported according to the STROBE guidelines.

## Author Contributions

M. Hensgens: contributed to the collection of the data and design of study and performed all analyses. Furthermore, she produced the first draft of the article. O. Dekkers: contributed to the epidemiological analyses and revised drafts of the article. A. Goorhuis: revised drafts of the article and collected parts of the data. S. Le Cessie: assisted with the statistical analyses and revised drafts of the article. E. Kuijper: designed the study and revised drafts of the article.

## Transparency Declaration

The Authors declare no conflicts of interest.

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